REMARKS

Applicants respectfully request entry of the amendments and remarks submitted herein. Claims 57, 66, 67, 69, 70, 79, 80, 82, 83, 92, 93, 95 and 96 have been amended, and claims 58-65, 68, 71-78, 81, 84-91 and 94 have been canceled without prejudice to continued prosecution. Claims 57, 66, 67, 69, 70, 79, 80, 82, 83, 92, 93, 95 and 96 are currently pending. Reconsideration of the pending application is respectfully requested.

The 35 U.S.C. §103 Rejections

Claims 57-64 and 67-69 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Ramisse et al. (1996, *FEMS Microbiology Letters*, 145:9-16), Makino et al. (1989, *J. Bacter.*, 171:722-730) and Buck et al. (1999, *Biotechniques*, 27:528-536). Claims 65 and 66 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Ramisse et al., Makino et al. and Buck et al. further in view of Wittwer et al (1997, *Biotechniques*, 22:130-138) and Qi et al (2001, *Appl. Env. Mcirobiol.*, 67:3720-3727). Claims 70-77 and 80-82 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Ramisse et al., Price et al. (1999, *J. Bacter.*, 181:2358-2362) and Buck et al. Claims 78 and 79 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Ramisse et al., Price et al. and Buck et al. further in view of Wittwer et al. and Qi et al. Claims 83-90 and 93-95 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Ramisse et al., Bragg et al. (1989, *Gene*, 81:45-54) and Buck et al. Claims 91 and 92 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Ramisse et al., Bragg et al. and Buck et al. further in view of Wittwer et al. and Qi et al. Claim 96 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Ramisse et al., Makino et al., Price et al., Bragg et al. and Buck et al.

Independent claim 57 has been amended to recite four different *capB* sequences, independent claim 70 has been amended to recite four different *pagA* sequences, and independent claim 83 has been amended to recite four different *lef* sequences, with each sequence including a length limitation. In addition, claims 69, 82 and 95 already recite four different capB, pagA or lef sequences, respectively, while claim 96 recites a combination of all

twelve sequences (four capB sequences, four pagA sequences and four lef sequences). Those claims have been amended to include a length limitation. None of the cited references, alone or in combination, teach or suggest the particularly claimed combination of sequences recited in independent claims 57, 69, 70, 82, 83, 95 and 96.

The Examiner is using Buck et al. as a reference that ostensibly provides both motivation and a reasonable expectation of success (i.e., that any oligonucleotide will work). Buck et al. is not relevant to the obviousness of the claimed methods, however, for a number of reasons. First, Buck et al. did not use any of the claimed nucleic acid sequences (e.g., *capB*, *pagA*, or *lef*) nor did Buck et al. use nucleic acid sequences from *Bacillus anthracis*. Also, even ignoring the fact that Buck et al. did not use *Bacillus anthracis* nucleic acids, an automated sequencing reaction as described in Buck et al. is significantly different than a PCR amplification reaction in which, generally, at least two oligonucleotides are used, or a real-time PCR amplification reaction in which, generally, three or four oligonucleotides are used. Using a single oligonucleotide in a sequencing reaction as Buck et al. does is vastly different than using two, three, or four oligonucleotides in a real-time PCR amplification reaction. The premise of Buck et al. *may* be true for sequencing reactions on the template DNAs reported therein, but it is certainly not true for amplification reactions, particularly real-time amplification reactions, on completely different template nucleic acids.

In addition, the results reported by Buck et al. using sequencing primers are not representative of results using different primer and probe sequences in various types of amplification reactions. Primer design for PCR amplification and primer and probe design for real-time PCR amplification frequently is not predictable. Applicants respectfully refer the Examiner to the copy of the guidelines published by the University of Chicago Cancer Research Center DNA Sequencing Facility, which states "...be aware that no set of guidelines will always accurately predict the success of a primer. Some primers may fail for no apparent reason, and primers that appear to be poor candidates may work well."

In addition, Applicants have provided several peer-reviewed publications with the November 7, 2005 IDS that compare different primer sets or compare the same primer set under different amplification conditions. For example, Csordas et al. states that "[p]rimers originally designed for end-point PCR did not have adequate specificity or sensitivity compared with those

specifically designed for real-time PCR" (see the Abstract); Elnifro et al. states that "[e]mpirical testing and a trial-and-error approach may have to be used when testing several primer pairs, because there are no means to predict the performance characteristics of a selected primer pair even among those that satisfy the general parameters of primer design" (first full sentence on page 560); Tichopad et al. states that "unknown tissue-specific factors can influence amplification kinetics but this affect can be ameliorated, in part, by appropriate primer selection" (see the Abstract); and Abd-Elsalam states that "...the most critical parameter for successful PCR is the design of primers" (see first full paragraph on page 94). These references support Applicants' assertion that all primers and probes are not equivalent and may not work in an amplification reaction.

Applicants are aware of no case law standing for the proposition that a longer sequence makes *per se* obvious specific primer and probe sequences from within that longer sequence. In fact, based on the current case law, each of the claimed primer and probe sequences is not obvious over the cited references, and certainly not the particularly recited combination of two, four, six or eight sequences. See, for example, *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992) ("[t]hat the claimed compound is a species of a genus disclosed in a prior art reference does not necessarily make the compound prima facie obvious") and *In re Bell*, 991, F.2d 781, 26 USPQ2d 1529 (Fed. Cir. 1993) ("given the nearly infinite number of possibilities suggested by the prior art, and the failure of the cited prior art to suggest which of those possibilities [to select], the claimed sequences would not have been obvious"). See, also, *In re Deuel* (51 F.3d 1552, 34 UPSQ2d 1210 (Fed. Cir. 1995)), which also stands for the non-obviousness of a sequence. Specifically, *In re Deuel* states that methods of isolating and making specific DNA molecules are not obvious over prior art that does not disclose the specific DNA molecules. The lack of motivation to select a particular DNA sequence from among numerous degenerate variants was a factor in determining the non-obviousness of the claims in *In re Deuel*.

There are a number of decisions including those discussed herein indicating that a species (in this case, a particular oligonucleotide) is not obvious over a very large genus (in this case, all possible fragments of the full-length sequence disclosed in the prior art to which the oligonucleotide has complementarity). Applicants note that much of the case law regarding the non-obviousness of a species over the prior art teaching of a genus containing such a species

(sometimes referred to as an 'invention of selection') is in the chemical arts. Significantly, the Courts have stated in several major opinions that DNA is a chemical. See, for example, *Amgen v. Chugai*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) ["a gene is a chemical compound"].

In addition, the combinations of the four different primer sequences recited in independent claims 57, 69, 70, 82, 83, 95 and 96 are not obvious because of secondary considerations. For example, the sequences disclosed in the present specification exhibit high sensitivity and specificity toward their respective targets. See, for example, Examples 1, 4 and 5 of the specification.

The current obviousness rejections of specific primer or probe sequences are not consistent with the standard for obviousness and with the current case law regarding obviousness. Applicants have provided evidence to refute the obviousness of the claimed combination of sequences and, in view of the amendments and the remarks herein, Applicants respectfully request that the rejection of the pending claims under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

Applicants respectfully request that claims 57, 66, 67, 69, 70, 79, 80, 82, 83, 92, 93, 95 and 96 be allowed. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: February 16, 2007

M. Angela Parsons, Ph.D.
Reg. No. 44,282

Fish & Richardson P.C.
60 South Sixth Street, Suite 3300
Minneapolis, MN 55402
Telephone: (612) 335-5070
Facsimile: (612) 288-9696